CASE REPORT

Tuberculous arthritis: negative Xpert MTB/RIF assay does not rule out infection!

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SUMMARY

We present a case of a 31-year-old man of Indian origin with no previous medical history who presented with an inflamed knee. Treatment for bacterial infection was unsuccessful, and needle aspiration of the left knee effusion/collection was smear and culture positive for tuberculosis (TB), despite Xpert MTB/RIF being falsely negative. The patient was commenced on quadruple therapy for TB and within 2 months had improved significantly with no clinical evidence of ongoing inflammation.

BACKGROUND

Tuberculosis remains a significant global health problem, causing 4000 deaths each day worldwide.¹ In the UK last year, there were 2679 cases of purely extrapulmonary TB (EPTB), of which 6.7% were in bone or joints unrelated to the spine.² As well as causing significant damage to the joint if left undiagnosed, untreated TB can lead to dissemination of infection.³ Therefore, prompt diagnosis is crucial. Due to the paucibacillary nature of non-pulmonary samples, appreciation of the limitations of diagnostic assays for identification of *Mycobacterium tuberculosis* (MTB) is important, particularly among non-infection specialists.

CASE PRESENTATION

A 31-year-old man of Indian origin presented to the emergency department with a 10-day history of pain, redness and swelling to his left thigh, which had increased despite taking ibuprofen for a week. He had difficulty walking but did not complain of fever or any other systemic symptoms. There was no history of insect bite or other injury. He was previously fit and well, took no regular medications and drank alcohol occasionally. He had recently returned from a 2-month holiday in India where he visited family. He was self-employed and lived at home with his wife. On examination, there was a 3–4 cm swelling superolateral to the left patella, which was erythematous (figure 1). The swelling was tender to palpation and warm to touch. There was no wound, no inguinal lymphadenopathy and the patient was able to fully weight-bear with difficulty. A clinical diagnosis of bacterial cellulitis was made and he therefore received 3 days of intravenous ceftriaxone, which made no difference to his symptoms.

INVESTIGATIONS

Routine blood tests showed normal renal and liver function with raised C reactive protein (40 mg/L)

and a mildly raised platelet count ($489 \times 10^9/L$). Chest radiograph was normal. An ultrasound scan of the thigh collection showed an area of liquefaction with an apparent wall, which was lying superficial to the vastus lateralis muscle measuring 4 cm in length (figure 2). The overlying subcutaneous fat showed inflammatory change, and there was the impression of a small tract extending caudally down to the lateral aspect of the knee joint. The left knee showed a small effusion, with similar complex echo content.

Needle aspiration of the left knee joint effusion through the suprapatellar pouch revealed cloudy and blood-stained fluid. On microscopy, white cells (++) and scanty acid-fast bacilli were seen with auramine staining. However, Xpert MTB/RIF was negative. An MRI of the knee showed a large abscess affecting the deep subcutaneous tissue around the left knee (figure 3 A, B). There was also a mild to moderate joint effusion.

TREATMENT

The patient was started on standard quadruple TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol with pyridoxine), and ceftriaxone was stopped. Subsequently, his Mantoux test was positive (measuring 18 mm) and MTB grew at 9 days, which was fully sensitive.

OUTCOME AND FOLLOW-UP

After 2 months of treatment, his knee felt almost back to normal and was no longer swollen. He was therefore stepped down to rifampicin and isoniazid and will complete 6 months of TB treatment in total.

DISCUSSION

Tuberculosis remains a significant global health problem, causing 4000 deaths each day worldwide.¹

In 2015, 5758 cases were diagnosed in the UK, 2679 of whom had purely extrapulmonary disease. Also, 6.7% of all cases of EPTB in the UK were found in bone or joints unrelated to the spine.² Tuberculous arthritis most frequently affects the larger weight-bearing joints such as the hip or (as in our case) the knee. It is usually monoarticular, of subacute onset, and joint effusions and/or associated collections are often described as cold abscesses, with swelling and only mild erythema and pain.³ Patients may or may not complain of systemic symptoms such as fever, night sweats and weight loss.⁴

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Figure 1 Photograph showing erythematous swelling above the left patella.

Tuberculous inflammation of a joint can cause significant damage with pathological fracture, cartilage destruction, deformity and associated disability.⁵ Radiological findings may initially show soft-tissue swelling, but later osteopenia, periosteal thickening and periarticular bone destruction. Ultimately, untreated TB at any site can lead to dissemination of infection and associated morbidity and/or mortality.⁶ Therefore, a high clinical suspicion is needed to ensure prompt diagnosis and initiation of treatment. Of note, tuberculous arthropathy should not be confused with Poncet's disease, which is a well-described reactive arthritis in the presence of extra-articular tuberculosis.

Traditionally, diagnosis of TB is by identification of acid-fast bacilli by light microscopy ('smear positivity') and/or culture of *Mycobacteria* from a body fluid or tissue sample ('culture positivity'). However, microscopy has low sensitivity, particularly in non-sputum samples, which are often paucibacillary.⁷ Culture

Figure 2 Echogenic, avascular collection superficial to vastus lateralis, with trace of peripheral flow seen on power Doppler.

has higher sensitivity but can take a long time. In our case, MTB was isolated relatively quickly after 9 days, but many samples take several weeks to culture.

Molecular testing for diagnosis of TB has been developed and is now widely available. The most commonly used PCR assay, Xpert MTB/RIF, is rapid and has high sensitivity for sputum samples (pooled sensitivity of 89% in an updated Cochrane Systematic Review,⁸ published in 2014).

In a recent meta-analysis of Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis, sensitivity (compared with culture) is reported as 83.1% for lymph node tissue, 80.5% for cerebrospinal fluid samples, yet only 46.4% for pleural fluid samples. This study did not include synovial fluid samples, highlighting the paucity of data in this area.⁹ A recent study reported sensitivity of PCR for MTB on knee joint tissue samples obtained at diagnostic arthroscopy to be 62.5%.¹⁰ In our case, despite the patient's joint fluid sample being smear and culture positive, MTB PCR was falsely negative. The newly developed Xpert MTB/RIF Ultra (Xpert Ultra) has been shown to have increased sensitivity when compared with Xpert MTB/RIF for pulmonary and cerebrospinal fluid samples, but this assay is not yet widely available.^{11 12}

There are various possible reasons for low sensitivity of TB PCR on synovial fluid in the diagnosis of tuberculous arthritis. The amount of MTB DNA in samples may be below the limit of detection of the test. This could be because of paucibacillary disease, degradation of organisms by phagocytosis or other components of the immune system, prior initiation of TB treatment (though this did not occur in our case) or degradation of samples during transport or storage. If a sample is of large enough volume, the concentration of genetic material can be increased by centrifuge. In our laboratory, it is standard procedure to centrifuge all samples and remove supernatant leaving 2–5 mL (in this case, at least 5 mL of synovial fluid was processed). Then 0.5 mL of the concentrate is added to 1.5 mL of molecular buffer, then added to the Xpert MTB/RIF cartridge. Bahr *et al* showed that centrifuged CSF samples optimised the diagnostic sensitivity of GeneXpert in the detection of TB meningitis, an effect which may transfer to synovial fluid.¹³ A systematic review by Maynard-Smith *et al* shows that sensitivity for lymph node and other tissue samples (including synovial tissue) is higher (0.88, 95% CI 0.76 to 0.94) in GeneXpert when compared with pleural fluid and other serous fluids (0.34, 95% CI 0.24 to 0.44).¹⁴

After the sample preparation and loading, problems with the XpertMTB/RIF assay itself could also cause false-negative results. For example, the extraction phase (where bacillary DNA is DNA that is separated from proteins, membranes and other cellular material) may not work or there may be inhibitors present in clinical samples that may hamper the PCR reaction itself. However, the Xpert MTB/RIF assay includes an internal control and therefore detects these faults and should result in a failed run.¹⁵

In summary, EPTB is often atypical in its presentation, and diagnosis can be challenging due to limitations in tissue sampling, paucibacillarity of samples and insensitive tests. Appreciation of the limitations of diagnostic assays for TB is important, in particular among non-infection specialists who may investigate patients with EPTB. Tuberculous arthritis often presents subacutely without systemic features and could be misdiagnosed as an inflammatory or crystal arthropathy, particularly if initial tests for TB are negative. Furthermore, attempted treatment of non-infectious arthropathy with steroids or other immunosuppressive therapy may do significant harm. Our patient likely benefited from early initiation of antituberculous therapy based

Figure 3 (A) Coronal IR (inversion recovery) sequence of the left knee. There is 9 cm high-signal, minimally complex lentiform collection superficial to and effacing vastus lateralis. There is oedema within the muscle. (B) Axial fat-saturated post-contrast sequence of the left knee following administration of extracellular gadolinium demonstrates peripheral enhancement of the collection.

largely on clinical presentation and smear positivity, and before MTB was confirmed by culture or molecular diagnostics.

Learning points

- ▶ Extrapulmonary tuberculosis (TB) is often atypical in its presentation; bone and joint disease can present subacutely with or without systemic symptoms.
- ▶ Appreciation of limitations in diagnostic assays for TB is important, particularly in non-sputum samples due to their paucibacillary nature.
- ▶ Early initiation of antituberculous therapy is crucial as delay can lead to destruction of the joint and ultimately disseminated infection.

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